



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07K 5/083, A61K 38/06, C12P 41/00, C07K 5/087, C07C 229/48		A3	(11) International Publication Number: WO 00/09543
			(43) International Publication Date: 24 February 2000 (24.02.00)
(21) International Application Number: PCT/CA99/00736			
(22) International Filing Date: 9 August 1999 (09.08.99)			
(30) Priority Data: 60/095,931 10 August 1998 (10.08.98) US 60/132,386 4 May 1999 (04.05.99) US			
(71) Applicant (for all designated States except US): BOEHRINGER INGELHEIM (CANADA) LTD. [CA/CA]; 2100 Cunard Street, Laval, Québec H7S 2G5 (CA).			
(72) Inventors; and (75) Inventors/Applicants (for US only): LLINAS-BRUNET, Montse [CA/CA]; 14 Rushbrooke, Dollard-Des-Ormeaux, Québec H9B 3K6 (CA). BAILEY, Murray, D. [CA/CA]; 344 Groulx, Pierrefonds, Québec H8Y 1B3 (CA). CAMERON, Dale [CA/CA]; 493 de l'Érablière, Rosemère, Québec J7A 4M4 (CA). FAUCHER, Anne-Marie [CA/CA]; 11 Lefebvre North, Oka, Québec J0N 1E0 (CA). GHIRO, Elise [CA/CA]; 768 Pierre, Laval, Québec H7X 3L8 (CA). GOUDREAU, Nathalie [CA/CA]; 416 Graham, Mont-Royal, Québec H3P 2C9 (CA). HALMOS, Teddy [CA/CA]; 1935 Jean Picard #8, Laval, Québec H7T 2K4 (CA). POUPART, Marc-André [CA/CA]; 101 Aimé Séguin, Vimont, Québec H7M 1B3 (CA). RANCOURT,			
		Jean [CA/CA]; 6400 de l'Aiglon, Laval, Québec H7L 4W2 (CA). TSANTRIZOS, Youla, S. [CA/CA]; 1590 Champigny, Saint-Laurent, Québec H4L 4P7 (CA). WERNIC, Dominik, M. [CA/CA]; 900 des Giroflées, Laval, Québec H7X 3G5 (CA). SIMONEAU, Bruno [CA/CA]; 2615 de la volière, Laval, Québec H7L 3V6 (CA).	
		(74) Agent: BERNIER, Louise, G.; Boehringer Ingelheim (Canada) Ltd., Patent Department, 2100 Cunard Street, Laval, Québec H7S 2G5 (CA).	
		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW. ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
		Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
		(88) Date of publication of the international search report: 25 May 2000 (25.05.00)	
(54) Title: HEPATITIS C INHIBITOR TRI-PEPTIDES			
(57) Abstract			
<p>Racemates, diastereoisomers and optical isomers of a compound of formula (I) wherein B is H, a C₆ or C₁₀ aryl, C₇₋₁₆ aralkyl; Het or (lower alkyl)-Het, all of which optionally substituted with C₁₋₆ alkyl; C₁₋₆ alkoxy; C₁₋₆ alkanoyl; hydroxy; hydroxyalkyl; halo; haloalkyl; nitro; cyano; cyanoalkyl; amino optionally substituted with C₁₋₆ alkyl; amido; or (lower alkyl)amide; or B is an acyl derivative of formula R₄-C(O)-; a carboxyl of formula R₄-O-C(O)-; an amide of formula R₄-N(R₅)-C(O)-; a thioamide of formula R₄-N(R₅)-C(S)-; or a sulfonyl of formula R₄-SO₂; R₅ is H or C₁₋₆ alkyl; and Y is H or C₁₋₆ alkyl; R³ is C₁₋₈ alkyl, C₃₋₇ cycloalkyl, or C₄₋₁₀ alkylcycloalkyl, all optionally substituted with hydroxy, C₁₋₆ alkoxy, C₁₋₆ thioalkyl, amido, (lower alkyl)amido, C₆ or C₁₀ aryl, or C₇₋₁₆ aralkyl; R₂ is CH₂-R₂₀, NH-R₂₀, O-R₂₀ or S-R₂₀, wherein R₂₀ is a saturated or unsaturated C₃₋₇ cycloalkyl or C₄₋₁₀ (alkyl)cycloalkyl, all of which being optionally mono-, di- or tri-substituted with R₂₁, or R₂₀ is a C₆ or C₁₀ aryl or C₇₋₁₄ aralkyl optionally substituted, or R₂₀ is Het or (lower alkyl)-Het, both optionally substituted, Het or (lower alkyl)-Het; carboxyl; carboxy(lower alkyl); C₆ or C₁₀ aryl, C₇₋₁₄ aralkyl or Het, said aryl, aralkyl or Het being optionally substituted; and R¹ is H; C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl, all optionally substituted with halogen; or a pharmaceutically acceptable salt or ester thereof.</p>			
		<p style="text-align: right;">(I)</p>	

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

Inter. nat. Application No

PCT/CA 99/00736

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K5/083 C07K5/087 A61K38/06 C07C229/48 C12P41/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K A61K C07C C12P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>WO 99 07733 A (BOEHRINGER INGELHEIM CA LTD ; RANCOURT JEAN (CA); SIMONEAU BRUNO (C) 18 February 1999 (1999-02-18)</p> <p>The whole document; see especially claims 12-15 and Table 4</p> <p style="text-align: center;">— — — — — — / —</p>	<p>1, 4, 10, 16-24, 26-29, 36, 37, 40, 66, 74, 78-81, 84-87</p>

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

Date of the actual completion of the international search

23 February 2000

Date of mailing of the international search report

29 MARCH 2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Groenendijk, M

INTERNATIONAL SEARCH REPORT

Inter. Appl. No.

PCT/CA 99/00736

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GAUCHER A ET AL: "Palladium (0) Catalyzed Tandem Alkylation and SN ² Cyclization of 1,4-Dichlorobut-2-ene by the N-(Diphenylmethylene)acetonitrile. A Stereoselective Synthesis of 1-Aminocyclopropanecarboxylic Acids" TETRAHEDRON LETTERS, NL, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 36, no. 17, page 2979-2982 XP004028172 ISSN: 0040-4039 page 2979	79
X	DE 196 00 034 A (HUELS CHEMISCHE WERKE AG) 3 July 1997 (1997-07-03)	79
Y	See page 4, formula 5, example 1; claim 2	82, 83
X	FLICHE E.A.: "Enantioselective synthesis of (1R,2S) and (1S,2S) dehydrocoronamic acid" SYNTHETIC COMMUNICATIONS, vol. 24, no. 20, 1994, pages 2873-2876, XP000857016	79
Y	the whole document	82, 83
Y	CHEN E.A.: "Chirally selective hydrolysis of D,L amino esters by alkaline protease" J.CHEM.SOC.CHEM.COMMUN., vol. 20, 1986, pages 1514-1516, XP002131118 the whole document	82, 83
Y	CHEN E.A.: "Kinetic resolution of esters of amino acids in t-butanol containing 5% water catalyzed by a stable industrial alkaline protease" CHIRALITY, vol. 6, 1994, pages 572-576, XP000876982 the whole document	82, 83
A	WO 98 17679 A (DEININGER DAVID D ; MURCKO MARK A (US); VERTEX PHARMA (US); FARMER) 30 April 1998 (1998-04-30) cited in the application the whole document	1-81, 84-87
	-/-	

INTERNATIONAL SEARCH REPORT

Intern. Patent Application No

PCT/CA 99/00736

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LLINAS-BRUNET M ET AL: "Peptide-based inhibitors of the hepatitis C virus serine protease" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 8, no. 13, page 1713-1718 XP004137115 ISSN: 0960-894X the whole document	1-81, 84-87
A	GERSHONOV E.A.: "1-Aminocyclobutanecarboxylic acid derivatives as novel structural elements in bioactive peptides: application to tuftsin analogs" JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, no. 24, 1996, pages 4833-4843, XP002123142 WASHINGTON US figure 1	
A	OGAWA, TOMOHISA ET AL: "2,3-Methanophenylalanine and.alpha.,.beta.- dehydrophenylalanine derivatives as chymotrypsin inhibitor" PEPT. CHEM. (1990), VOLUME DATE 1989, 27TH, 379-82, XP000856307	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 99/ 00736

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 67-72 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
Claims: 74-77, 80, 81, 84 (all partially)

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 74-77,80,81,84(all partially)

Present claims 74-77,80,81 and 84 relate to a process for the preparation of a (serine) protease analog without defining a structure having said activity.

The application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for (the preparation of) only a very limited number of such compounds, that is the compounds defined by the formula of claim 1. In the present case, said claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the prepared products by reference to a result to be achieved, that is their activity.. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search for the subject-matter of said claims 74-77,80,81 and 84 has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the preparation of compounds of the formula I of claim 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-81,84-87

Compounds of formula I of claim 1, their preparation and use; compounds of claim 79 and their use in the preparation of compounds of formula I

2. Claims: 82,83

Process for the resolution of enantiomers as defined in the claims 82 and 83

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Application No

PCT/CA 99/00736

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9907733 A	18-02-1999	AU 8795698 A	01-03-1999
DE 19600034 A	03-07-1997	NONE	
WO 9817679 A	30-04-1998	AU 5147798 A	15-05-1998
		BR 9712544 A	19-10-1999
		CZ 9901340 A	11-08-1999
		EP 0932617 A	04-08-1999
		NO 991832 A	17-06-1999
		PL 332872 A	25-10-1999